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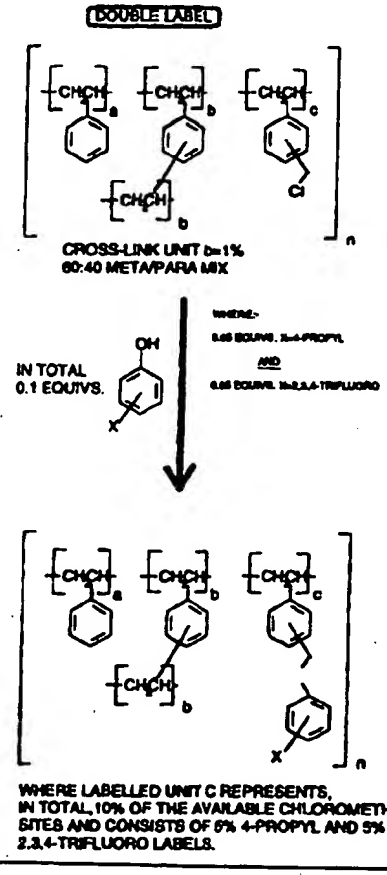
(57) Abstract

A method for the preparation of a labelled chemical library which method comprises synthesizing the library on a plurality of solid supports each of which is provided with at least one inert label which label remains attached to the solid phase and is unaffected by library synthesis, so as to provide a chemical library comprising a plurality of solid supports to each of which is attached at least one inert label and at least one member of the chemical library.



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CHEMICAL LIBRARIES ; LABELLING AND DECONVOLUTION THEREOF.

Chemical libraries may be assembled by a number of methods. including the 'combine/mix/divide' process described by Furka et al (Abstr. 14th Int.Congr.Biochem.. Prague. Czechoslovakia. 1988. 5. 47: Int.J.Pept.Prot.Res. 1991. 37. 487-493) for creating libraries on polymer beads. in which each bead contains one discrete chemical species. The individual components of the library may be tested either still attached to the polymer bead on which they were synthesised (Lam et al. Nature. 1991. 354. 82-84) or after cleavage from the bead (Salmon et al. Proc.Nat.Acad.Sci.USA. 1993. 11708-11712). If tested while attached to the bead. or cleaved but physically associated with the bead. it is necessary to devise a method of identifying the chemical which is bound to any bead found to be biologically active in the test. Where this compound is a polypeptide this may be achieved by Edman degradation. either directly or after cleavage from the bead (Lam et al. Bioorg.Med.Chem.Lett., 1993, 419-424); oligonucleotides may be identified by microsequencing techniques (Dower et al, Ann.Rep.Med.Chem.. 1991. 26. 271-280).

Researchers have attempted to identify peptides containing unnatural amino acids (which are not amenable to Edman degradation) by co-synthesising a second peptide chain comprising natural amino acids and using this as a sequenceable 'code' (Nikolaiev et al. Peptide Research. 1993. 6. 161-170), and others have used oligonucleotide chains as 'codes' to identify the other ligands (Needels et al. Proc.Nat.Acad.Sci.USA. 1993. 90. 10700-10704), while mixtures of halogenated acids have been used. incorporated in trace amounts at each stage of the synthesis. to form an identifiable (by gas chromatography) 'binary code' system for ligand definition (Borchardt and Still. J.Am.Chem.Soc.. 1994. 116. 373-374). These methods have been reviewed extensively (Jacobs and Fodor. TIBTECH. 1994. 12. 19-26). Pavia et al (Eds). Bioorg. and Med.Chem.Lett.. 1994. 381-470). Moos et al. Ann.Rep.Med.Chem.. 1993. 28. 315-324. Gordon et al. J.Med.Chem.. 1994. 37. 1233-1251. and 1386-1401).

We have now devised a novel method for labelling a chemical library wherein one or more inert labels are attached to the beads prior to and/or during chemical library synthesis and are not modified under the conditions of chemical library synthesis.

Therefore in a first aspect of the invention we provide a method for the preparation of a labelled chemical library which method comprises synthesising the library on a plurality of solid supports each of which is firstly provided with at least one inert label, so as to provide a chemical library comprising a plurality of solid supports to each of which is attached at least one inert label and at least one member of the chemical library.

Suitable inert labels are species which remain attached to a solid support during library synthesis but are not modified. Synthesis of the chemical library may comprise any convenient number of individual reaction steps.

Convenient inert labels for attachment include phenols, such as substituted phenols, thiophenols, such as substituted thiophenols, bicyclic phenols, such as substituted naphthols, biaryl phenols, such as substituted arylphenols, polycyclic phenols, such as substituted hydroxy-phenanthrenes and -anthracenes, hydroxy- and mercapto-substituted heterocycles, such as hydroxy- or mercapto-pyridines, -quinolines and -indoles, alcohols, such as substituted alcohols, arylalcohols, such as substituted benzylalcohols, phenylsilanols, such as substituted phenylsilanols, and silanols, such as substituted silanols.

Preferred inert labels are phenols, such as substituted phenols, thiophenols such as substituted thiophenols, bicyclic phenols, such as substituted naphthols, and biarylphenols, such as substituted biarylphenols. Suitable substituents include alkyl groups (including straight or branched chain C1-C20, C1-C12, C1-C6 and C1-C4 alkyl groups) and inert substituents such as one or more halogen groups (including Cl, Br, F and I). Also included are halogenated alkyl groups wherein the halogen and alkyl groups are as indicated above. The inert label(s) may be removed, for identification purposes, once library synthesis is complete. Identification is effected using any convenient analytical technique. Conveniently the inert label is cleaved and detected for example by gas chromatography-mass spectrometry (GC-MS) or by liquid chromatography-mass spectrometry (LC-MS).

Examples of substituted phenols suitable for use in the present invention are: 3-Me; 3-F; 3-Et; 3-Cl; 3,5-di-F; 4-Pr; 3-F,4-Cl; 4-sec-Bu; 4-Cl,3,5-di-Me; 3,5-di-Cl; 3-Br. These are just a few of the many possible choices.

The solid supports are conveniently beads, such as resin beads, or any species which may be used in chemical library synthesis, for example in combine/mix/divide processes. The solid support is either inherently adapted, by way of its chemical structure, for

reaction with the chemical compounds or is pre-treated. By way of example a plurality of solid supports such as polystyrene beads is provided with chloromethyl, and/or aminomethyl and/or hydroxymethyl groups. Inert label(s) may be attached using appropriate chemistry to these groups. Chloromethyl resins such as chloromethyl polystyrene beads are a particularly preferred solid support.

By way of non-limiting example chloromethylpolystyrene beads are labelled by reaction with small amounts (for example 5-10%) of simple phenols containing inert substituents such as halogen and alkyl groups. in the presence of a base such as sodium methoxide. Furthermore. if a mixture of for example two primary label phenols is used then a large number of combinations is possible for a relatively small number of phenols.

A library is then created. for example by the 'combine/mix/divide' or 'split synthesis' technique (Furka et al. opcit), utilising the remainder of the chloromethyl groups. then subsequent isolation of a bead which shows biological activity may be followed by identification of the substituent introduced last by reference to the reaction which produced it, as no 'mix' stage will have been done. Cleavage of the label(s) from the active bead allows identification of the batch of resin used for the first stage of the synthesis. and hence the nature of the first substituent used. Knowing these two substituents (first and last) limits the number of possible structures to a level where they may be identified by, for example. mass spectrometry or iterative resynthesis.

In a further aspect of the invention we provide a method for the preparation of a labelled chemical library which method comprises synthesising the library on a plurality of solid supports each of which is firstly provided with at least one primary inert label. and introducing during library synthesis at least one further secondary inert label. so as to provide a chemical library comprising a plurality of solid supports to each of which is attached at least one primary inert label. at least one secondary inert label and at least one member of the library.

The secondary inert label is conveniently introduced by controlled modification of groups which form part of the one or more primary labels. Such group(s) include bromo. iodo and trifluoromethanesulphonyloxy groups. Most convenient are bromo and iodo. These particular groups are conveniently presented on the solid support via substituted

phenols. thiophenols. naphthols. arylphenols. aromatic hydroxy- or mercapto-heterocycles. aralkyl alcohols and phenylsilanols as defined hereinbefore. which are attached to the solid support by such methods as are also outlined above. Preferred moieties are bromophenols. iodophenols. bromonaphthols. iodonaphthols and bromo- or iodo-arylphenols. Particularly preferred moieties are 3-bromophenol. 4-bromophenol. 3-iodophenol. 4-iodophenol. 6-bromo-2-naphthol and 4-(4'-bromophenyl)phenol.

In addition. the secondary inert label may be introduced via other groups present on the solid support.

We refer to the above groups as latent groups, that is to say they are inert with respect to compound library synthesis. but may participate in the introduction of one or more inert secondary labels during library synthesis. The particular chemistry which is used selectively to modify these latent groups and so introduce the secondary inert labels constitutes a further important aspect of this disclosure and is detailed hereinbelow.

The one or more secondary labels are conveniently introduced during library synthesis by for example such procedures as palladium-, nickel- or copper-catalysed cross-coupling reaction with an organometallic reagent. for example an arylboronate. an organostannane. organozinc or organolithium reagent. in a so-called Heck. Stille or Suzuki coupling reaction (see for example Deshpande. Tetrahedron Lett.. 1994. 35. 5613-4; Yu. et al. Tetrahedron Lett.. 1994. 35. 8919-22: Frenette and Friesen. Tetrahedron Lett.. 1994. 35. 9177-80: Forman and Sucholeiki. J. Org. Chem.. 1995. 60. 523-8). Again if a mixture of for example two secondary labels is used then a large number of combinations is possible for a relatively small number of secondary labels.

The preferred synthesis of the secondary label is via a metal-catalysed cross-coupling reaction. Particularly preferred is the palladium-catalysed cross-coupling of an arylboronic acid to a latent group in a so-called Suzuki coupling, where the intermedium moiety attached to the solid support is one of 3-bromophenol. 4-bromophenol. 3-iodophenol, 4-iodophenol. 6-bromo-2-naphthol or 4-(4'-bromophenyl)phenol. Preferred secondary inert labels include substituted phenols, naphthols or arylphenols. Suitable phenol, naphthol or arylphenol substituents include alkenyl, alkynyl and aryl, especially phenyl, heterocyclyl and bicyclyl, and substituted aryl, especially substituted phenyl, heterocyclyl and bicyclyl. Suitable aryl substitutents include chloro. fluoro. alkyl (C1-C4), alkoxy, aryl, trifluoromethyl and mixtures of these. for example (methylfluorophenyl)phenol. The secondary inert label(s)

may be removed, for identification purposes, once library synthesis is complete. Identification is effected using any convenient analytical technique. Conveniently the secondary inert label(s) is(are) cleaved along with the primary inert label(s) as detailed above, and detected simultaneously by, for example, GC-MS or LC-MS.

By way of non-limiting example, chloromethylpolystyrene beads are derivatised by reaction with small amounts, between 1% and 20%, such as between 1 and 10%, and preferably between 2% and 10%, such as between 2 and 5%, of between 1 and 5 phenols for each library sub-pool. These phenols are conveniently chosen from a set of between 5 and 50, and preferably between 5 and 20 primary label phenols, which contain inert substituents such as halogen and alkyl groups together with a small amount, between 1 and 20% and preferably between 5% and 10%, of a phenol containing a latent group, for example bromo or iodo, in the presence of a base such as sodium methoxide. If a mixture of for example two primary phenols containing inert substituents (each for example at 5-10%), together with one phenol containing a latent group (for example at 5-10%) is used, then a large number of combinations is possible for a relatively small number of phenols. If a library is now created, for example by utilising the remainder of the chloromethyl groups, and by a combine/mix/divide or split synthesis technique, wherein a particular inert label or labels designate a particular primary library substituent that has been added in the first round of synthesis, and wherein a particular secondary inert label or labels, which have been derived from the latent group, designate a particular intermediate library substituent that has been added in an intermediate round of synthesis, then subsequent isolation of a bead which shows or is associated with biological activity may be followed firstly by identification of the library substituent introduced in the last round of synthesis by reference to the reaction which produced it, as no 'mix' stage will have been performed, then secondly by cleavage of the primary and secondary inert labels from the active bead to allow identification, from the primary inert label(s), of the batch of resin used for the first stage of the synthesis, and hence the nature of the primary library substituent which was added in the first round of synthesis, and, from the secondary inert label(s), of the particular intermediate-round chemistry, and hence the nature of the substituent from that particular round of synthesis. Knowing these three substituents (first, intermediate and last) limits the number of possible

biologically active library structures to a level where they may be identified directly, or in the case of there being more than two 'mix' steps in the combine/mix/divide or split synthesis, by, for example, mass spectrometry or iterative resynthesis.

The chemical library may comprise any convenient number of individual members, for example tens to hundreds to thousands to millions etc., of suitable compounds, for example peptides, peptoids and other oligomeric compounds (cyclic or linear), and template-based smaller molecules, for example benzodiazepines, hydantoins, biaryls, polycyclic compounds (eg. naphthalenes, phenothiazines, acridines, steroids etc.), carbohydrate and amino acid derivatives, dihydropyridines, benzhydryls and heterocycles (eg. triazines, indoles etc.). The numbers quoted and the types of compounds listed are illustrative, but not limiting.

Preferred library compounds are chemical compounds of low molecular weight and potential therapeutic agents. They are for example of less than about 1000 daltons, such as less than 800, 600 or 400 daltons.

Synthesis of the compound library on the solid supports may comprise any convenient number of individual reaction steps.

Any convenient biological of interest such as a receptor, enzyme or the like may be contacted with the chemical library as above in an assay or test system apparent to the scientist of ordinary skill. In this regard it will be appreciated that the inert label or labels may not interact with the biological of interest to any significant extent.

Chemical libraries prepared according to the method of the invention are novel and in a further aspect of the invention we provide a chemical library comprising a plurality of solid supports to each of which is attached at least one inert label and at least one member of the chemical library. Convenient solid supports and inert labels are as disclosed above. In a still further aspect we provide a chemical library comprising a plurality of solid supports to each of which is attached at least one inert primary label, at least one inert secondary label and at least one member of the chemical library.

The labels may be cleaved from the resin by treatment with a suitable cleavage agent, for example boron tribromide, or iodotrimethylsilane, or hydrogen together with a suitable metal catalyst, or a strong acid such as hydrogen fluoride (HF) or hydrogen bromide (HBr), either in the form of a vapour or dissolved in a suitable solvent, and optionally in the presence of suitable scavengers. This list of cleavage agents is illustrative

but not limiting. Particularly preferred is HBr dissolved in acetic acid (AcOH). Use of this cleavage agent gives a mixture of the phenol labels and their acetates. In one particular modification of the invention a cleavage agent mixture of HBr. AcOH. acetic anhydride. and p-hydroxyphenylacetic acid is used. The acetic anhydride ensures conversion of all the phenols to their acetates. thus simplifying the identification procedure. although identification is still possible without its use. The p-hydroxyphenylacetic acid is used as a scavenger to remove the traces of bromine normally present in HBr. as this can cause the formation of bromophenols during label excision. After cleavage the mixture is treated with excess sodium or potassium bicarbonate solution. extracted with ethyl acetate. and the extract analysed by a suitable analytical technique. such as mass spectrometry (MS), or by linked analytical techniques. such as gas chromatography (GC)-MS or liquid chromatography (LC)-MS. in order to identify the label(s).

The invention will now be illustrated by reference to the following non-limiting Examples and Figures in which:

Figure 1 outlines the covalent attachment of a single. substituted phenol label to a chloromethylpolystyrene polymer.

Figure 2 outlines the covalent attachment of a double. substituted phenol label to a chloromethylpolystyrene polymer.

Figure 3 outlines the chemical cleavage of substituted phenol labels. as their O-acetates. from the polymers illustrated in Figures 1 and 2.

Example 1

Single Label (3-bromophenol):

A suspension of chloromethylated polystyrene resin beads (5 g, BIO-RAD, Bio-Beads S-X1, chloromethylated, 200-400 mesh, capacity 4.15 meq./g 1% cross-linked) in N,N-dimethylformamide (DMF) (42 mL dried over 4A molecular sieve) was stirred and purged with inert gas at ambient temperature for 20 minutes. Sodium methoxide (0.11 g, 0.1 equivalents) was added, followed by a solution of 97% 3-bromophenol (0.37 g, 0.1 equivalents) in DMF (3 mL, dried over 4A molecular sieve). The mixture was stirred at 50°C for 18 hours under an atmosphere of inert gas. The resin was collected by vacuum filtration and washed successively with DMF (4 times), dioxan (4 times), 1:1 dioxan/water (6 times), dioxan (4 times) and methanol (4 times). The resin so obtained was dried to constant weight under vacuum at ambient temperature to afford 5.17 g.

Elemental Analysis found: Cl, 13.2%; Br, 3.1%; labelling at 10% level requires: Cl, 13.2%; Br, 3.0%.

Example 2

Single label (4-propylphenol):

To a suspension of poly(chloromethylstyrene) (5 g, Polymer Laboratories, PL-CMS Resin, 150-300 micron, capacity 3.5 meq/g) in dry DMF (50 mL) under inert gas at room temperature, was added in turn 4-propylphenol (2.76 mL) and 95% sodium methoxide (1.08 g). The resultant reaction mixture was heated to 50°C and stirred at that temperature under an inert atmosphere for 18 h. The reaction mixture was allowed to cool to room temperature, then the resin was collected by filtration and washed successively with DMF (twice), water (once), DMF (3 times), DMF/water, 2:1 (3 times), THF (3 times), methanol (once), THF (twice), methanol (twice) and finally ether. The resin obtained was dried under high vacuum to afford 5.5 g of singly labelled material.

Elemental Analysis found: C, 82.5%; H, 7.3%; Cl, 6.5%; labelling at 40% level requires: Cl, 6.53%. This gives resin with a chlorine substitution of 1.83 meq/g.

Example 3

Double Label (4-propylphenol & 2,3,4-trifluorophenol):

A suspension of poly(chloromethystyrene) resin beads (5 g, Polymer Laboratories, PL-CMS Resin, 150-300 micron, capacity 4.0 meq./g) in dry DMF (42 mL) was swirled and purged with inert gas at ambient temperature for 5 minutes. Sodium methoxide (0.11 g, 0.1 equivalents) was added, followed by a solution of 4-propylphenol (0.14 g, 0.05 equivalents) and 2,3,4-Trifluorophenol (0.15 g, 0.05 equivalents) in DMF (4ml, dried over 4A molecular sieve). The mixture was shaken at 50°C for 72 hours under an atmosphere of inert gas. The resin was collected by vacuum filtration and washed successively with DMF (4 times), dioxan (4 times), 1:1 dioxan/water (6 times), and methanol (4 times). The resin so obtained was dried to constant weight under vacuum at ambient temperature to afford 5.31 g.

Elemental Analysis found: C, 77.6%; H, 6.8%; Cl, 10.9%; F, 1.2%.

Example 4

Double Label (4-propylphenol & 3-bromophenol):

To a suspension of the 40%-labelled resin prepared in Example 2 (4.5 g) in dry DMF (40 mL) under an inert atmosphere was added 3-bromophenol (4.15 g) and 95% sodium methoxide (1.4 g). The resultant mixture was shaken at 50°C under an inert atmosphere for 3 days. The reaction mixture was allowed to cool to room temperature, then the resin was collected by filtration, washed according to the protocol described in Example 2 and dried under high vacuum to give 5.5 g of doubly labelled material.

Elemental Analysis found: C, 78.0%; H, 6.9%; Cl, 0%; Br, 9.1%. This gives a resin with a bromine substitution of 1.14 meq/g.

Example 5

Suzuki Coupling:

To a suspension of the doubly labelled resin prepared in Example 4 (0.5 g) in dimethoxyethane (DME: 6 mL) under an inert atmosphere was added in turn, water (0.6 mL), potassium fluoride (176 mg), 4-chlorophenylboronic acid (325 mg) and tetrakis(triphenylphosphine)palladium (0) (30 mg). The resultant mixture was heated to 90°C and stirred at that temperature overnight.

The reaction mixture was then allowed to cool to room temperature and the resin was collected by filtration, washed successively with DME (twice), a 20% mixture of DME in 10% aqueous ammonia (5 times), DME (once), THF (twice), methanol (once), THF (once), methanol (twice) and finally ether (twice), then dried under high vacuum to give 0.5 g of doubly labelled material (4-propylphenol & 3-(4-chlorophenyl)phenol).

Elemental Analysis found: C, 82.5%; H, 6.9%; Cl, 3.8%; Br, 0%. This gives a resin with a chlorine substitution of 1.07 meq/g. Quantitative replacement of bromine by 4-chlorophenyl requires: Cl, 3.9%.

Example 6

Cleavage of labels from resin and subsequent identification:

One single bead of doubly-labelled resin (prepared as disclosed in Example 3) was placed in a small siliconised vial. A solution of 4-hydroxyphenylacetic acid (50 mg) and acetic anhydride (0.1 mL) in 33% hydrogen bromide in glacial acetic acid (1 mL), which had been previously prepared and allowed to stand at ambient temperature for 2.5 hours, was added to the bead (4 drops, sufficient only to wet the bead). The mixture was allowed to stand at ambient temperature for 24 hours. A 20% solution of potassium hydrogen carbonate in water

was added dropwise until the mixture was neutralised. The solution was extracted once with ethyl acetate (analytical grade, very small volume) to afford a clear organic solution which contained the two cleaved labels (4-propylphenol and 2,3,4-trifluorophenol) as their O-acetates. These were clearly identified by GC-MS.

Example 7

Cleavage of labels from resin and subsequent identification:

One single bead of doubly labelled resin prepared as in Example 5 was processed according to the method of Example 6. Analysis of the resultant clear organic solution by GC-MS clearly identified the primary label, 4-propylphenol and the secondary label, 3-(4-chlorophenyl)phenol both as their O-acetates (M+, 178 and 246/248 respectively), along with the free phenols (M+, 136 and 204/206 respectively).

Claims:

1. A method for the preparation of a labelled chemical library which method comprises synthesising the library on a plurality of solid supports each of which is provided with at least one inert label. so as to provide a chemical library comprising a plurality of solid supports to each of which is attached at least one inert label and at least one member of the chemical library.

2. A method for the preparation of a labelled chemical library which method comprises synthesising the library on a plurality of solid supports each of which is provided with at least one primary inert label. and introducing during library synthesis at least one secondary inert label. so as to provide a chemical library comprising a plurality of solid supports to each of which is attached at least one primary inert label. at least one secondary inert label and at least one member of the library.

3. A method as claimed in claim 2 wherein the secondary inert label is introduced by chemical modification of one or more of the primary inert labels.

4. A method as claimed in claim 3 wherein the primary inert label to be modified comprises a group selected from bromo. iodo and trifluoromethanesulphonyloxy.

5. A method as claimed in claim 3 or claim 4 wherein the one or more secondary labels are introduced via metal-catalysed cross-coupling reaction(s).

6. A method as claimed in any one of the previous claims wherein the primary inert label is a substituted phenol or thiophenol.

7. A method as claimed in claim 6 wherein the secondary inert label is a substituted alkenyl-, alkynyl-. or aryl-phenol or a substituted alkenyl-. alkynyl-. or aryl-thiophenol.

8. A method as claimed in any one of the previous claims wherein the

plurality of solid supports are polystyrene beads with chloromethyl, and/or aminomethyl and/or hydroxymethyl groups.

9. A method as claimed in any one of the previous claims wherein the chemical library comprises at least ten chemical compounds each having a molecular weight of less than 1000 daltons.

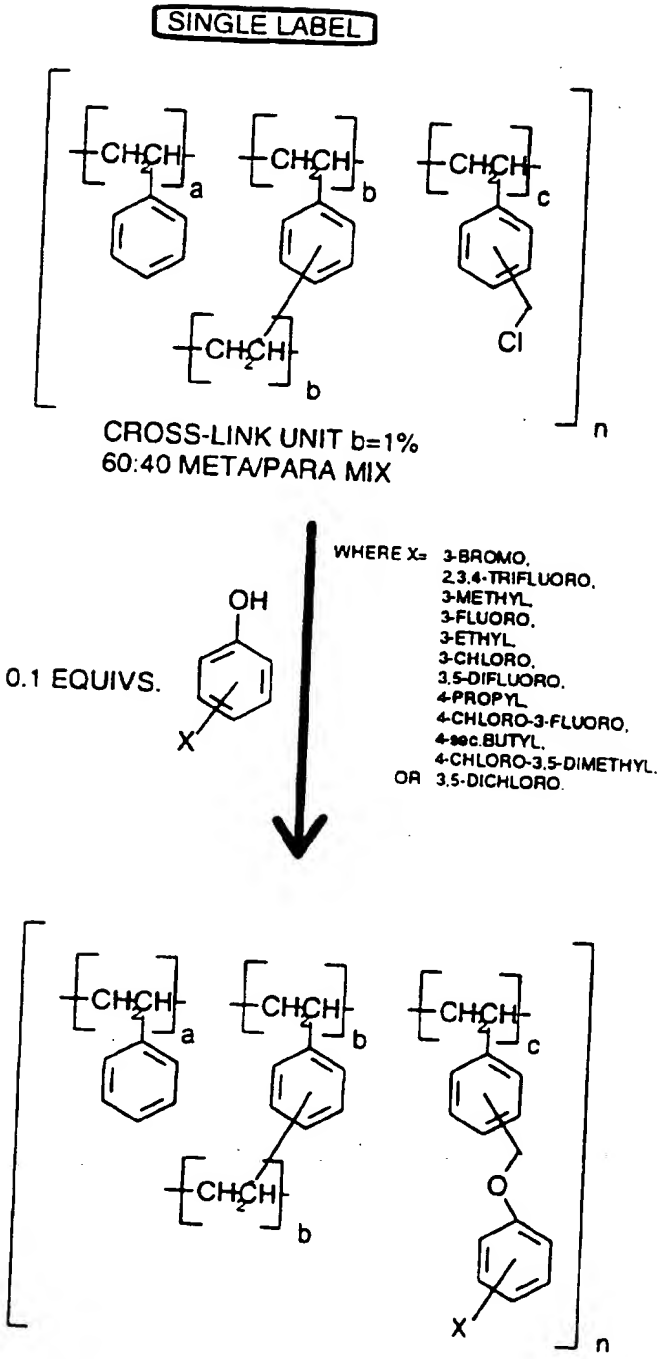
10. A labelled chemical library as prepared by the method of any one of claims 1-9.

11. The use of a labelled chemical library as claimed in claim 10 in biological assays, test systems or screens.

12. A method for the deconvolution of a library as claimed in claim 10 which comprises cleaving primary and/or secondary inert label(s) from solid supports of interest and identifying the label(s) using mass spectrometry.

13. A method as claimed in claim 12 which comprises identifying the cleaved label(s) using gas chromatography or liquid chromatography linked to mass spectrometry.

FIGURE 1


SINGLE LABEL
a
b
c
b
Cl
n
CROSS-LINK UNIT b=1%
60:40 META/PARA MIX
0.1 EQUIVS.
OH
X
WHERE X= 3-BROMO,
2,3,4-TRIFLUORO,
3-METHYL,
3-FLUORO,
3-ETHYL,
3-CHLORO,
3,5-DIFLUORO,
4-PROPYL,
4-CHLORO-3-FLUORO,
4-sec.BUTYL,
4-CHLORO-3,5-DIMETHYL,
OR 3,5-DICHLORO.
a
b
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O
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WHERE LABELLED UNIT C REPRESENTS
10% OF THE AVAILABLE CHLOROMETHYL
SITES

FIGURE 2

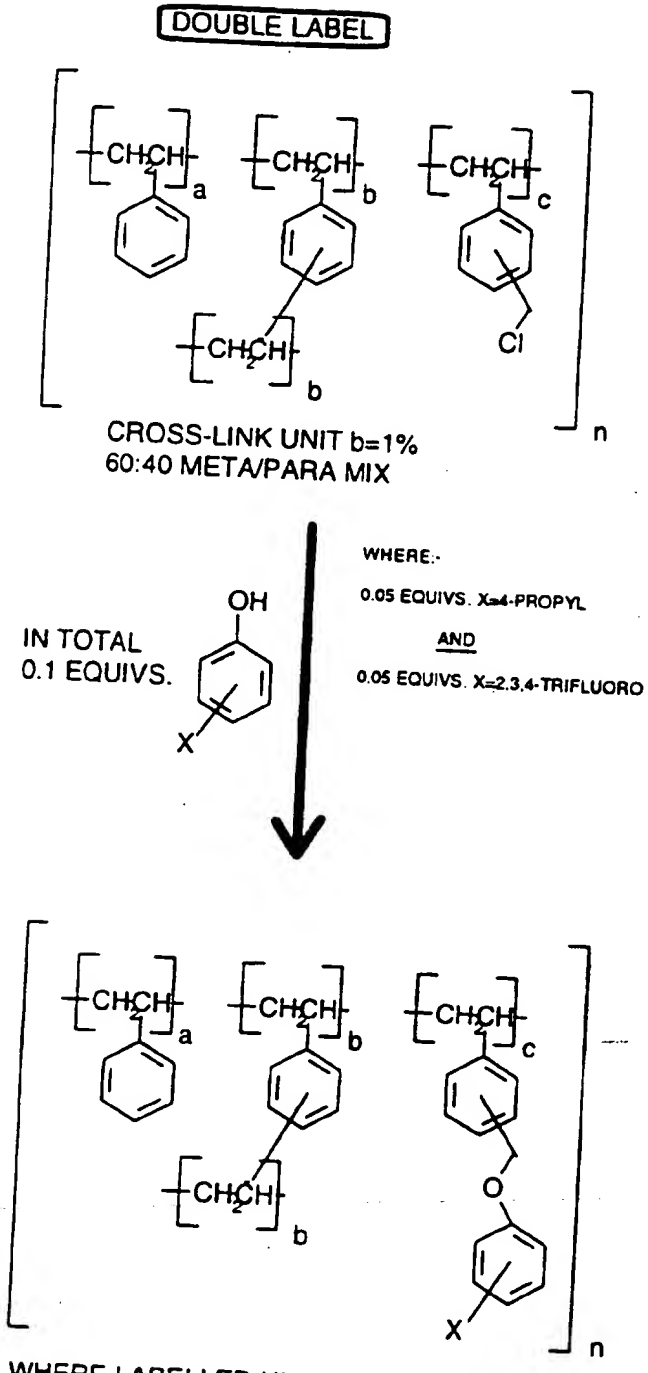
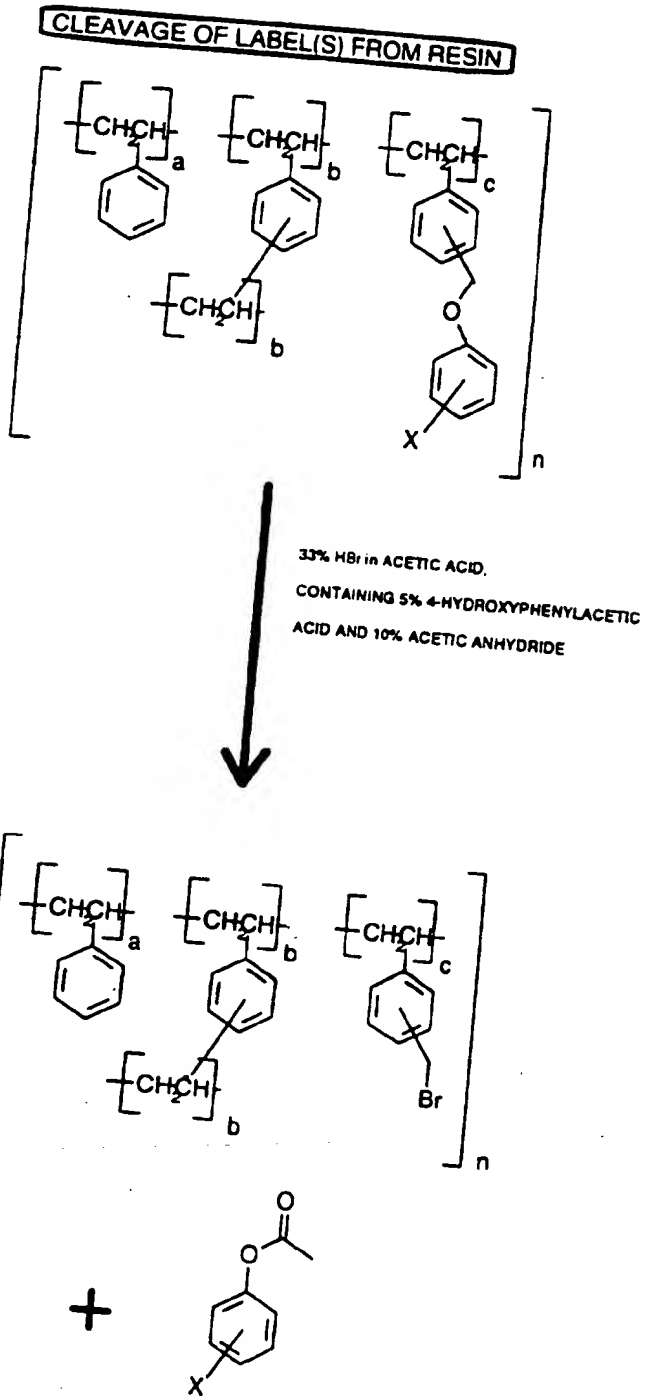

DOUBLE LABEL
CROSS-LINK UNIT b=1%
60:40 META/PARA MIX
IN TOTAL
0.1 EQUIVS.
WHERE:-
0.05 EQUIVS. X=4-PROPYL
AND
0.05 EQUIVS. X=2,3,4-TRIFLUORO
WHERE LABELLED UNIT C REPRESENTS,
IN TOTAL,10% OF THE AVAILABLE CHLOROMETHYL
SITES AND CONSISTS OF 5% 4-PROPYL AND 5%
2,3,4-TRIFLUORO LABELS.

FIGURE 3


CLEAVAGE OF LABEL(S) FROM RESIN
33% HBr in ACETIC ACID,
CONTAINING 5% 4-HYDROXYPHENYLACETIC
ACID AND 10% ACETIC ANHYDRIDE
Br
WHERE X= 3-BROMO, 2,3,4-TRIFLUORO, 3-METHYL, 3-FLUORO,
3-ETHYL, 3-CHLORO, 3,5-DIFLUOR , 4-PROPYL,
4-CHLORO-3-FLUORO, 4-sec.BUTYL, 4-CHLORO-3,5-
DIMETHYL OR 3,5-DICHLOR

INTERNATIONAL SEARCH REPORT

International Application No
PL./GB 96/00197

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07B61/00 G01N33/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07B C12Q C07K C07H G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 13623 (CHIRON CORP) 23 June 1994 see the whole document ---	1-3,6-13
X	WO,A,92 00091 (BIOLIGAND INC) 9 January 1992 see page 35, line 5-31 ---	1,2,9-11
X	WO,A,93 24517 (FURKA ARPAD ;SEBESTYEN FERENC (HU)) 9 December 1993 see examples 3-5,21,22 ---	1,9-11
X	WO,A,94 08051 (UNIV COLUMBIA ;COLD SPRING HARBOR LAB (US); STILL W CLARK (US); OH) 14 April 1994 see page 115 - page 125	1,2,6-13
Y	see page 115 - page 125 --- -/--	3,4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 July 1996	0 8. 07. 96

Name and mailing address of the ISA	Authorized officer
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Form PCT ISA 210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PC./GB 96/00197

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	TETRAHEDRON LETTERS, vol. 35, 1994, pages 9177-9180, XP002006025 R. FRENETTE AND R. FRIESEN: "Biaryl Synthesis via Suzuki Coupling on a Solid Support" cited in the application see the whole document -----	3,4

3

INTERNATIONAL SEARCH REPORT

International Application No
PC./GB 96/00197

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